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## Advanced applications of cerium oxide based nanozymes in cancer

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Cerium oxide nanozymes have emerged as a new type of bio-antioxidants in recent years.  $\text{CeO}_2$  nanozymes possess enzyme mimetic activities with outstanding free radical scavenging activity, facile synthesis conditions, and excellent biocompatibility. Based on these extraordinary properties, use of  $\text{CeO}_2$  nanozymes has been demonstrated to be a highly versatile therapeutic method for many diseases, such as for inflammation, rheumatoid arthritis, hepatic ischemia-reperfusion injury and Alzheimer's disease. In addition to that,  $\text{CeO}_2$  nanozymes have been widely used in the diagnosis and treatment of cancer. Many examples can be found in the literature, such as magnetic resonance detection, tumour marker detection, chemotherapy, radiotherapy, photodynamic therapy (PDT), and photothermal therapy (PTT). This review systematically summarises the latest applications of  $\text{CeO}_2$ -based nanozymes in cancer research and treatment. We believe that this paper will help develop value-added  $\text{CeO}_2$  nanozymes, offering great potential in the biotechnology industry and with great significance for the diagnosis and treatment of a wide range of malignancies.

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## Introduction

Enzymes are proteinaceous biomolecules with high specificity and high catalytic efficiency to their substrates. Natural enzymes may present some disadvantages, such as unstable properties, low biological content, high price, *etc.* However, with the rapid development of nanoscience, nanozymes have attracted the attention of many scholars and clinicians, as they can improve the stability of natural enzymes as well as reduce production costs.<sup>1</sup> Cerium oxide nanoparticles (CeNPs) are considered a promising candidate in nanomedicine due to their redox regulation and enzyme-like activity.<sup>2</sup> CeNPs have been shown to mimic a range of natural redox enzymes, including superoxide dismutase (SOD)<sup>3</sup> and catalase (CAT),<sup>4</sup> which remove detrimental reactive oxygen species (ROS) from the body.

Cerium has two different oxidation states in nature,  $\text{Ce}^{3+}$  and  $\text{Ce}^{4+}$ , and the enzymatic activity of  $\text{CeO}_2$ - $x$  scavenging ROS is thought to be due to the self-regeneration cycle of  $\text{Ce}^{3+}/\text{Ce}^{4+}$  and the oxygen vacancy on the cerium oxide surface<sup>5</sup> (Fig. 1). Most researchers considered that the antioxidant property of  $\text{CeO}_2$ - $x$  is closely related to  $\text{Ce}^{3+}/\text{Ce}^{4+}$  redox cycling. The potential role of oxygen vacancies in the fast redox cycling of  $\text{CeO}_2$ - $x$  is a center of debate as well.<sup>6</sup> X-ray photoelectron spectroscopy analysis

suggested a reliable dependence of  $\text{Ce}^{3+}/\text{Ce}^{4+}$  ratio on the size of ceria nanoparticles, which can reach as high as 44% for 3 nm nanoceria.<sup>3</sup> This ratio changes as a result of ROS-nanoceria interaction suggesting the possibilities of the fast redox cycling to the judge of  $\text{CeO}_2$ - $x$  redox activities.

It is widely recognized that cancer is a major worldwide public health problem with few effective treatment choices, poor prognosis, and high mortality rates.<sup>6</sup> Nanotechnology has emerged as the latest approach to diagnose and treat cancer, and CeNPs are a great candidate as they exhibit an exceptional

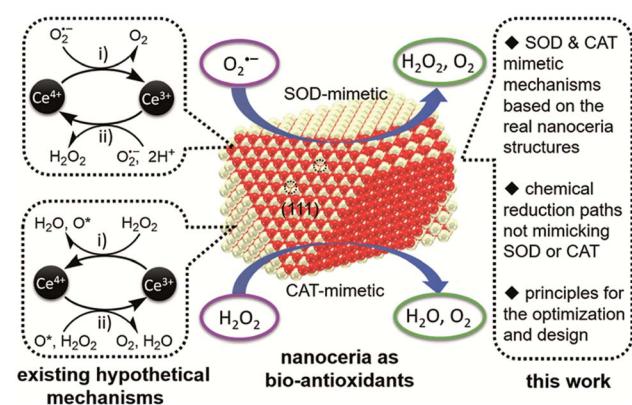


Fig. 1 Schematic illustrating the bio-antioxidant activity of nanoceria (middle), mechanisms hypothesized for it by drawing an analogy with those of natural superoxide dismutase (SOD) and catalase (CAT). Reproduced from ref. 5 with permission from the Royal Society of Chemistry.

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potential as a catalyst and antioxidant. Nanostructured metal oxides have a large surface area, good reactivity, high sensitivity, and specificity. Hence, they can be used to prepare nano-sensors to detect biomarkers, such as cancer-related proteins,<sup>7</sup> ctDNA,<sup>8</sup> etc. In particular, CeNP-based sensors present several advantages, such as good biocompatibility and high chemical stability. At present, resistance has become a serious challenge for anticancer therapies. In general, drug resistance mechanisms in tumours can be divided into three categories: inadequate pharmacokinetics, intrinsic factors of cancer cells, and tumour microenvironments (TMEs).<sup>9</sup> Nanoparticles are specific and effective in delivering drugs to target cells, tissues or organs, reducing drug resistance and minimizing the risk of side effects.<sup>10</sup> Furthermore, hypoxia is an essential factor in the formation of multidrug resistance, recurrence, and metastasis in solid tumours.<sup>11</sup> Recent studies have shown that CeNPs with catalase activity can catalyze H<sub>2</sub>O<sub>2</sub> to produce oxygen, improving the hypoxia of the TMEs to execute a synergistic anticancer effect. It is reported that CeNPs are protective as antioxidants in the neutral pH environment of normal cells, whereas they are toxic as pro-oxidants in the acidic pH environment of cancer cells.<sup>12</sup> Therefore, CeNPs have great potential in cancer treatment as both cytotoxic and protective agents. In addition, there is growing evidence that pro-oxidants are increasingly seen as potential chemotherapeutic drugs due to the high base levels of ROS in cancer cells<sup>13–15</sup> (Fig. 2). In conclusion, CeNPs have a broad application prospect in the diagnosis and treatment of cancer.

On this account, we elucidate the application of CeNPs in cancer diagnosis and treatment. By sharing a brief personal overview about the challenges and perspectives in CeNPs-based biomedical application, we expect that this review will open new research orientations for CeNPs-related theranostics.

### Application of nanoparticles in cancer diagnosis

Early diagnosis of cancer offers the best opportunity for appropriate therapeutic intervention strategies and significantly increases the success rate of treatment and recovery. Imaging, haematology pathology and genetics are the main techniques used in oncology, and the specificity and sensitivity of the examination tools are vital for accurate cancer detection. Abundant oxygen vacancy on the surface of CeNPs is reported to be suitable for use as a nanometer contrast agent for imaging

examination.<sup>16</sup> CeNPs can significantly immobilize enzymes or proteins on the surface of biological electrodes and improve the electron transfer efficiency between electrodes and electrode surface modified materials. Due to their biocompatibility, high chemical stability, excellent electron transfer capability, large surface area, strong adsorption capacity and catalytic performance, CeNPs can be used to prepare the substrate for immune biosensors and electrochemical DNA biosensors. It has been reported that some researchers have used CeNPs-based biosensors to detect cancer biomarkers. For example, CeNPs can be used as a luminescent material to detect carcinoembryonic antigen (CEA),<sup>17</sup> improving the sensitivity of the immune sensor to detect tumour-specific growth factor (TSGF) through its catalytic properties<sup>18</sup> and be used for electrochemical biosensor detection of the BCR/ABL fusion gene.<sup>19</sup> According to the above illustrations, CeNPs are widely used in medicine, and they deserve further research and development. Table 1 summarises some examples of CeNPs applications in the detection of tumour markers.

Currently, diffusion-weighted imaging combined with dynamic contrast-enhanced perfusion-weighted imaging (DWI/DCE-PWI) technology is used to detect cancer microvessel permeability and water diffusion to assess the degree of cancer malignancy. Before DCE-PWI examination, it is necessary to use gadolinium (Gd) chelate to improve the sensitivity of DWI. Still, the Gd-DTPA commonly used in clinical practice can cause MRI artefacts and is not sensitive enough. Chulun Shao *et al.* developed gadolinium doped (CeO<sub>2</sub>:Gd) CeO<sub>2</sub> nanoparticles as contrast agents.<sup>16</sup> The lattice oxygen vacancies on the surface of CeO<sub>2</sub>-x not only combine with a large number of water molecules to increase the *R*<sub>1</sub> value but also limit the diffusion motion of water molecules to further enhance the DWI signal and high-sensitivity detection on the tumour vascular microenvironment.<sup>16</sup> Therefore, CeNPs provide a new method for the design of magnetic resonance contrast agents.

Tumour markers have crucial practical value in screening, diagnosis, and efficacy evaluation.<sup>20,21</sup> Carcinoembryonic antigen (CEA) is one of the most well-known tumour markers as it is overexpressed in many cancers, especially colorectal cancer.<sup>22</sup> Xuehui Pang *et al.*<sup>17</sup> synthesized a chemiluminescent immunosensor based on GO/MWCNTs-COOH/Au-CeO<sub>2</sub>-x nanocomposite. The immunosensor showed satisfactory performance in CEA analysis of human serum samples, demonstrating high sensitivity and excellent repeatability. Tumour specific growth factor (TSGF) is a novel tumour marker, and it was reported to be significantly increased in the early stage of malignant tumours.<sup>23</sup> Siqi Yu *et al.* modified TSGF antigen and AB2-Ag@CeO<sub>2</sub>-x onto the electrode surface and designed a super-sensitive electrochemical immune sensor for the detection of TSGF.<sup>18</sup> Under optimal conditions, the immune sensor has a wide linear range, low detection limit, good repeatability, selectivity, and stability. As an early diagnosis marker of various cancers, squamous cell carcinoma antigen (SCCA) has a remarkable specificity of up to 90–96%. SCCA is mainly used as a tumour marker to diagnose squamous cell carcinoma, including cervical cancer.<sup>24</sup> SCCA should be diluted before detection, so high-sensitivity immunoassay is of great

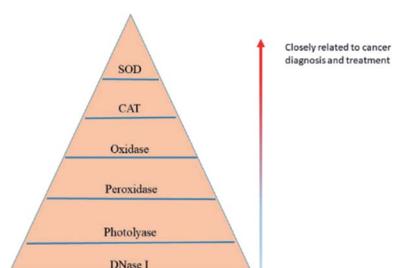


Fig. 2 Summarization of the discovered enzyme mimetic activities of CeNPs and the correlation with cancer diagnosis and treatment.



Table 1 A review of detection methods for tumor markers based on CeNPs

Markers	Features	Nanoparticle	Years (reference)	Broad linear range	Detection limit
CEA	Electrochemical immunosensor	GO/MWCNTs-COOH/Au@CeO <sub>2</sub>	2015 (ref. 17)	0.05–100 ng mL <sup>-1</sup>	0.02 ng mL <sup>-1</sup>
TSGF	Electrochemical immunosensor	Ab2-Ag@CeO <sub>2</sub>	2016 (ref. 18)	0.500–100 pg mL <sup>-1</sup>	0.2 pg mL <sup>-1</sup>
SCCA	Electrochemical immunosensor	Co <sub>3</sub> O <sub>4</sub> @CeO <sub>2</sub> -Au@Pt	2017 (ref. 25)	100 fg mL <sup>-1</sup> to 80 ng mL <sup>-1</sup>	33 fg mL <sup>-1</sup>
Cyfra-21-1	Electrochemical immunosensor	ncCeO <sub>2</sub> -RGO	2018 (ref. 27)	0.625 pg mL <sup>-1</sup> to 0.01 ng mL <sup>-1</sup>	0.625 pg mL <sup>-1</sup>
CA19-9	Electrochemical immunosensor	CeO <sub>2</sub> /FeO <sub>x</sub> @mC	2019 (ref. 29)	0.1–10 U mL <sup>-1</sup>	10 μU mL <sup>-1</sup>

significance for early detection of SCCA. Yueyun Li and colleagues made an ultrasensitive electrochemical immunosensor for quantitative detection of SCCA using Co<sub>3</sub>O<sub>4</sub>@CeO<sub>2</sub>-Au@Pt nanocomposite as enzyme-mimetic labels with low detection limit rate and wide linear range.<sup>25</sup> Among various oral cancer biomarkers, cytokeratin fragment-21-1 (Cyfra-21-1) has vital clinical applications due to its high concentration in the saliva samples of the patients.<sup>26</sup> Namrata Pachauri *et al.* used CeNPs cubes (ncCeO<sub>2</sub>)-reduced graphene oxide (RGO) based nanocomposite to detect Cyfra-21-1 (ref. 27) that showed improved sensitivity and detection compared with the previous work. The cancer marker carbohydrate antigen 19-9 (CA19-9) achieved the highest sensitivity and specificity in patients with pancreatic cancer.<sup>28</sup> Minghua Wang *et al.* successfully developed an electrochemical immune sensor based on nanometer CeO<sub>2</sub>-x for sensitive detection of CA19-9.<sup>29</sup> The immune sensor based on nanometer CeO<sub>2</sub>-x shows outstanding reproducibility, high selectivity, and stability. Human serum sample analysis results are satisfactory and have a broad application prospect in clinical tumour monitoring.

With the development of biomedical research on genetic diseases, DNA sequence detection has attracted more and more attention, especially in cancer diseases. Electrochemical methods have been widely used to detect DNA hybridisation due to their simplicity, low cost, and high sensitivity.<sup>30</sup> Ke-jun Feng *et al.* developed an effective DNA fixation matrix based on the nanoparticle CeO<sub>2</sub>-x/chitosan composite membrane to manufacture colorectal cancer DNA biosensors.<sup>31</sup> The biosensor is characterized by high detection sensitivity and wide linear range and can perfectly identify complementary target sequences and tetra-base mismatched sequences. Shengfeng Li *et al.* developed an effective DNA electrochemical biosensor for the detection of BCR/ABL based on gold nanoparticles (GNP) synthesized *in situ* on the surface of multi-walled carbon nanotubes (MWCNT), CeO<sub>2</sub>-x and Chitos composite membranes.<sup>19</sup> The detection of the BCR/ABL gene is of great significance for the early diagnosis, prognosis and assessment of chronic myelogenous leukaemia (CML) patients.<sup>32</sup> This method has been successfully used to detect real PCR samples with favourable selectivity, stability, and reproducibility.

### Application of nanoparticles in cancer treatment

Antitumour therapies include traditional surgery, chemotherapy, and radiation therapy, as well as emerging immunotherapies, targeted therapies, photodynamic therapy (PDT) and photothermal therapy (PTT). In terms of drug delivery systems, CeNPs with pharmacological potential can be used as

nanocarriers. Studies have shown that CeNPs halt the invasion of tumor cells by preventing the formation of myofibroblasts, a key component of cancer progression.<sup>33</sup> CeNPs can also cause the death of cancer cells by increasing the production of ROS.<sup>34</sup> The mimetic activity of CeNPs such as SOD, catalase, DNase I, photolysase, oxidase and peroxidase endows the ability of CeNPs to regulate ROS levels, leading to their exploration for the enhancement of PDT and PTT. Moreover, the dual capabilities to act as an oxidant in cancer cells, yet antioxidant in normal cells, makes the role of CeNPs as an adjuvant for radiation therapy (RT) which will dramatically benefit the patient quality of life.<sup>33</sup> It is reported that CeO<sub>2</sub>-x leads to DNA fragmentation by enhancing the production of ROS and ultimately leads to cell apoptosis through the p53-dependent mitochondrial signalling pathway.<sup>14</sup> It is worth mentioning that CeNPs are protective as antioxidants in neutral pH environments of normal cells,<sup>12</sup> whereas they are toxic as pro-oxidants in acidic pH environments of cancer cells. Therefore, CeNPs can be used as cytotoxic drugs and protective agents, which has great potential in cancer treatment. To summarise, CeNPs have many functions in tumour therapy and has significant application value. Table 2 summarises some examples of CeNPs application in oncology.

### Chemotherapy

Chemotherapy remains one of the most critical cancer treatments, but its effectiveness is often compromised by the rising incidence of multidrug resistance (MDR).<sup>35</sup> The hallmarks of the TME are hypoxia, high H<sub>2</sub>O<sub>2</sub> concentration, glucose deficiency and low pH value, all of these directly affecting the chemotherapy effect and outcome of the treatment.<sup>36</sup> In addition, chemotherapy has various well-known side effects that affect the patient's lifestyle, such as hair loss, bone marrow suppression, mucositis, nausea, and vomiting. Therefore, a compromise between killing the cancer cells and minimising the side effects on the system is the critical goals to be achieved. Among carriers for chemotherapy, CeNPs have been characterised by good biocompatibility, low cytotoxicity, and unique catalytic properties that make it a preferable choice for drug loading.

Wu *et al.* found that CeNPs can act as a chemical sensitiser because the pre-treated cells enhance the toxicity of the chemotherapy drug doxorubicin (DOX).<sup>37</sup> The intrinsic mechanism is that ROS produced by the CeNPs reduces the mitochondrial membrane potential (MMP), leading to the disruption of the mitochondrial function to inhibit chemotherapeutic drug efflux, and CeNPs consumes GSH to reduce DOX detoxification. In addition, CeNPs are more chemically



Table 2 Anti-tumor applications of CeNPs in tumor therapy

Treatment	Nanoparticle	Nanoparticle size (nm)	Years (reference)	Mainly role
PDT + chemotherapy	MSN-HP-DOX@CeO <sub>2</sub>	100	2016 (ref. 39)	Nanocarrier
PDT + chemotherapy	PPCNPs-Ce6/FA	36.1	2019 (ref. 40)	Nanocarrier
PDT	HA@CQDs-Ce6	3–5	2018 (ref. 41)	Radiation-protective and nanocarriers
PDT + PTT	Bi <sub>2</sub> S <sub>3</sub> @Ce6–CeO <sub>2</sub> NC	280–340	2020 (ref. 42)	Produce oxygen and nanocarrier
PTT + chemotherapy	Ru@CeO <sub>2</sub> -RBT/Res-DPEG	78	2020 (ref. 43)	Produce oxygen and nanocarrier
Radiotherapy	NGA-CNPs	3–5	2019 (ref. 44)	Radiation-protective agent and nanocarrier
Radiotherapy	CuS@CeO <sub>2</sub>	3–5	2020 (ref. 45)	ROS scavengers and nanocarrier
Chemotherapy	DNR-CeO <sub>2</sub> /TiO <sub>2</sub> NPs	9.12	2020 (ref. 46)	Nanocarrier
Chemotherapy	C-TherMod	<25	2018 (ref. 47)	Synergistic anticancer

sensitive to cancer cells than to normal cells, reducing the side effects due to the loss of healthy tissue. Xu *et al.* developed DOX loaded hollow CeNPs coated with polydopamine (PDA) and ammonium bicarbonate ( $\text{NH}_4\text{HCO}_3$ ) (Fig. 3). Under laser irradiation, the PDA shell would be destroyed due to the hyperthermia effect induced by the conversion of light into heat with PDA. The DOX and CeNPs would be released after PDA destruction. On the one hand, CeNPs could enhance the chemotherapy effect of DOX, as discussed above. On the other hand, CeNPs could also degrade hydrogen peroxide into hydroxyl radical to elicit chemodynamic therapy.<sup>38</sup> Besides, another research used cerium doped titanium dioxide nanoparticles ( $\text{CeO}_2\text{-x}/\text{TiO}_2\text{NPs}$ ) to form DNR- $\text{CeO}_2\text{-x}/\text{TiO}_2\text{NPs}$  complexes as a drug delivery system (DDS) for daunorubicin (DNR). Test results in B lymphocyte cultures showed that this DDS was superior to  $\text{TiO}_2$  NPs alone, and it had good biocompatibility and load efficiency, increasing drug accumulation in cells.<sup>46</sup> Pro-oxidants are increasingly seen as potential

chemotherapy drugs because of the high base levels of reactive oxygen species (ROS) in cancer cells. It is well known that the normal tissue microenvironment is neutral and the TMEs is acidic, and CeNPs plays a pro-oxidant role in the acidic micro-environment.<sup>12</sup> Studies have shown that  $\text{CeO}_2\text{-x}$  induces apoptosis in human colorectal cancer cell lines but has no effect on normal cells.<sup>14</sup> Christos Tapeinos *et al.* developed a pH-sensitive drug delivery system consisting of calcium carbonate and Type I collagen, loaded with CeNPs and the anticancer drug adriamycin. This system showed an enhanced therapeutic effect on osteosarcoma SaOS-2 cells and reduced toxicity on cardiac myoblasts H9C2 compared to adriamycin alone.<sup>47</sup> At a pH of 6.0, the synergistic effect of the oxidant CeNPs and encapsulated adriamycin resulted in almost 100% cell death, even at the lowest concentrations of the drug. Ying Zhang *et al.* coated dithio-polydopamine (PDS) on the porous  $\text{CeO}_2\text{-x}$  nanorod (CeONPs) surface to prepare a new drug delivery carrier capable of carrying DOX, which was then coupled to the surface of the nanorod using a lactose derivative (lac-NH<sub>2</sub>).<sup>48</sup> pH is one of the few factors proved to drive whether CeNPs act as oxidants or antioxidants. The antioxidant abilities of CeNPs have also resulted in the exploration of these particles as a promising therapy for cancer. Therefore, pH is a vital factor for CeNPs' appearance as nontoxic in normal cells due to various pH in normal cells compared to tumour cells.<sup>49</sup> In the specific microenvironment of cancer cells, such DDS can be used as nanocarriers and degrade PDS through high GSH concentration and low pH to expose cytotoxic CeONRs to cancer cells and have a synergistic anticancer effect on malignant cells.<sup>48</sup>

Notably, the effect of nanoparticles depends on the dose, application time, nanometer diameter, cell type, intracellular environment, *etc*.<sup>50,51</sup> Furthermore, the toxicity of CeNPs is dose-dependent and time-dependent in cancer cells.<sup>34</sup> However, studies have shown that high doses of CeNPs may promote the proliferation of hepatocellular carcinoma cells in a dose-dependent manner.<sup>50</sup> Therefore, the selection of CeNPs in cancer treatment should consider various circumstances.

### Radiotherapy

Radiotherapy (RT) is a clinically effective treatment strategy for malignancies, with more than half of all tumours suitable for radiotherapy.<sup>52</sup> The main mechanism of radiotherapy is DNA

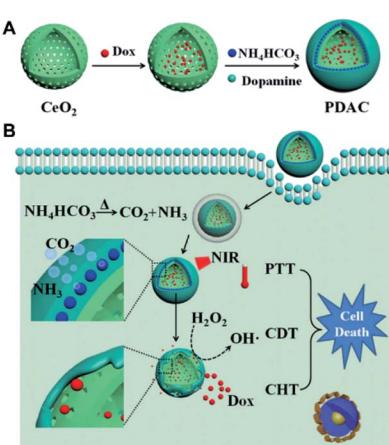


Fig. 3 (A) Schematic illustrating the design and synthesis of PDAC NPs for tumor therapy. The preparation process of PDAC NPs. (B) The synergic effect among PTT, chemodynamic therapy and chemotherapy of cancer: under NIR laser irradiation, PDA shell firstly generates the photothermal performance, subsequently leading to the shell collapse and exposed  $\text{CeO}_2\text{-x}$  surface, which can catalyze  $\text{H}_2\text{O}_2$  into hydroxyl radical for chemodynamic therapy, meanwhile the leakage of PDA shell can further release DOX to present chemotherapy against cancer. Reproduced from ref. 38 with permission from Springer Nature.



damage, including direct ionization damage and indirect induction by stimulating ROS production.<sup>53</sup> However, radiation resistance and damage to normal tissue are the cardinal obstacles to be overcome. Hypoxia-induced resistance to radiotherapy is a pivotal factor in radiation resistance.<sup>54</sup> CeNPs can catalyse endogenous  $H_2O_2$  to  $O_2$  in malignant tissues, thus re-modelling the anoxic microenvironment to an RT-sensitive environment. Therefore, Zhou *et al.* designed a multiple radiosensitisation strategy to resist the main causes of radioresistance, such as hypoxia in the tumour microenvironment and upregulation of DNA repair proteins.<sup>55</sup> By anchoring CeNPs on the surface of a novel 2D graphdiyne (GDY), the fabricated GDY-CeNPs could exhibit desirable CAT activity to catalyse  $H_2O_2$  into  $O_2$  to alleviate hypoxia. Simultaneously, through encapsulation of miR181a in the nanosystem, the sensitivity of RT could be enhanced by targeting the RAD17 and Chk2 pathways (Fig. 4).

In addition, by regulating the number of antioxidant enzymes and ROS, CeNPs have been reported to provide nearly 99% protection against radiation-induced cell death in normal cells but not in tumour cells.<sup>56,57</sup> Studies have shown that CeNPs can protect the gastrointestinal epithelium from radiation damage<sup>56</sup> and prevent radiation-induced pneumonia<sup>57</sup> or dermatitis.<sup>58</sup> Therefore, CeNPs are an ideal material for radiosensitiser and radioprotectant. The experimental results suggested a striking effect of these nanocomposites in overcoming hypoxia-induced radioresistance and in the therapy of oesophageal squamous cell carcinoma (ESCC) both *in vivo* and *in*

*vitro*.<sup>55</sup> Further studies have shown the use of CeNPs before RT can significantly enhance the apoptosis of cancer cells and inhibit the growth of pancreatic tumours in mice without damaging healthy tissues.<sup>59</sup> A novel radiation sensitisier (NGA-CNPs) was synthesised by coating ceria nanoparticles (CNPs) with the anticancer drug neogambogic acid (NGA).<sup>44</sup> Compared with RT alone, NGA and CNPs, the combined application of NGA-CNPs and RT has better clinical effects and reduces damage to surrounding tissues. Wei Jiang *et al.* synthesised spindle-shaped CuS@CeO<sub>2</sub>-x core-shell nanoparticles that could be used in combination with PTT/RT therapy for hypoxic tumours.<sup>45</sup> CeO<sub>2</sub>-x alters the anoxic tumour environment, while CuS nanoparticles encapsulated in CeO<sub>2</sub>-x undergo stable release and deep tissue penetration. *In vitro* and *in vivo* studies have shown that CuS@CeO<sub>2</sub>-x not only reduces the dose of RT but, more importantly, enables the entire tumour to be treated without recurrence. In short, as a kind of auxiliary material for RT, CeNPs have a broad application prospect in clinical treatment.

### Photodynamic therapy and photothermal therapy

As a novel strategy for cancer treatment, PDT involves light, photosensitisers (PSs), and oxygen and has excellent potential in treating drug-resistant malignancies. The mechanism of PDT is that the PSs accumulated in tumour cells are stimulated by light at appropriate wavelengths and transfer photon energy to biological substrates to produce ROS, which destroys

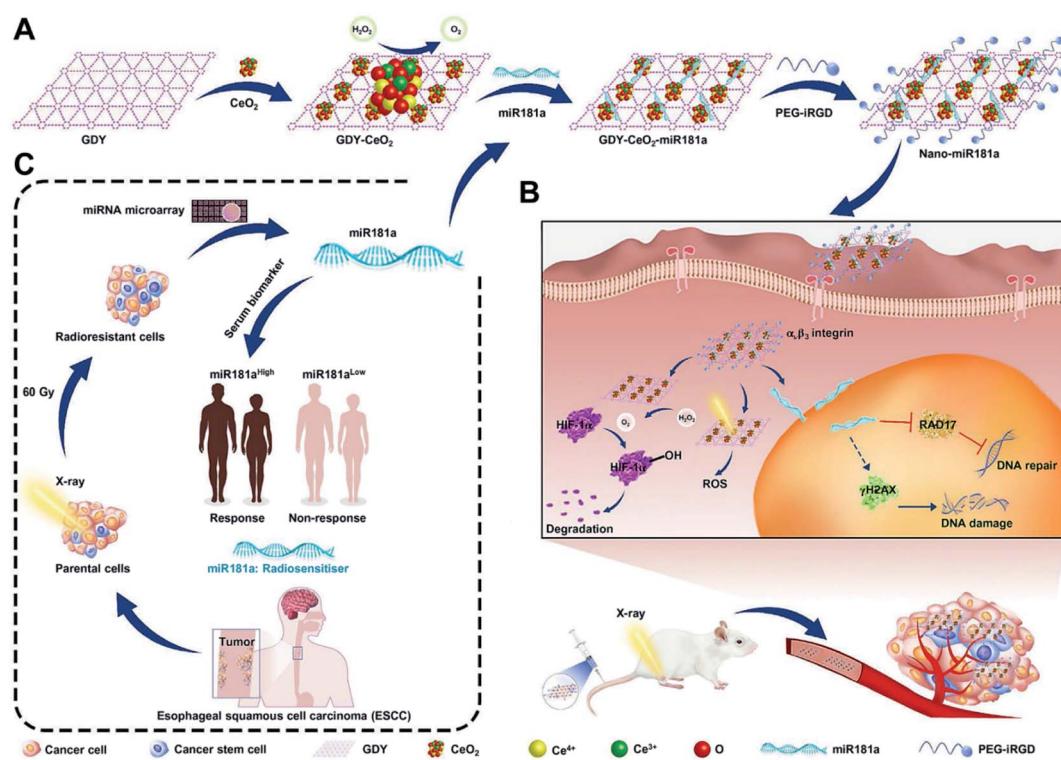


Fig. 4 (A) Schematic illustration of the successive synthetic procedures of the multiple radiosensitizer with catalase activity, (B) enhancing intracellular radiation deposition, (C) and RNA interference for the highly efficient radiotherapy of ESCC. Reproduced from ref. 55 with permission from John Wiley and Sons.



biomolecules and eventually causes the destruction and death of tumour cells.<sup>60,61</sup> The number of PSs in tumours is directly related to ROS generation; thus, the effective localization of PSs in tumours is crucial. Some limitations of clinical application of PDT include low PSs delivery efficiency, poor targeting, and hypoxic environment in tumours. Due to its spontaneous circulation between  $\text{Ce}^{3+}$  and  $\text{Ce}^{4+}$  in the redox reaction,  $\text{CeO}_2\text{-x}$  can react with the high level of endogenous  $\text{H}_2\text{O}_2$  in tumour cells to generate  $\text{H}_2\text{O}$  and  $\text{O}_2$  simultaneously.<sup>62,63</sup> At the same time, the increased surface area, selective targeting, and long cycle time of CeNPs increase the effectiveness of PSs delivery, thus improving the utility of PDT. Porphyrin derivatives and chloramphenicol e6 (Ce6) are typical PSs of PDT,<sup>64,65</sup> but their poor water solubility and low targeting ability severely limit their applications *in vivo*. Researchers have designed a response system based on CeNPs coated DOX and photosensitised hemoporphyrin (HP) double-loaded mesoporous silica nanoparticles (MSN).<sup>39</sup> After entering into cancer cells, the high concentration of intracellular glutathione and low pH environment will reduce CeNPs to cerium ions. With the degradation of CeNPs and conformational changes of HP under light irradiation, pre-loaded DOX is released. This change exacerbates its cytotoxicity on cancer cells (Fig. 5). Hong Li *et al.* synthesised a novel drug delivery platform based on chlorin e6 (Ce6)/folic acid (FA)-loaded branched polyethylenimine-PEGylation CeNPs (PPCNPs-Ce6/FA) to overcome drug-resistant breast cancer *via* targeted PDT.<sup>40</sup> The nanosystem promotes cell uptake of PSs with the assistance of CeNPs and FA, resulting in better tumour inhibition. A recent report<sup>41</sup> illustrated that  $\text{H}_2\text{O}_2$  assisted HA@ceria nanoquantum dots (HA@CQDs-Ce6/

$\text{H}_2\text{O}_2$ ), a unique particle synthesised with hyaluronic acid (HA) and CeNPs on its surface, increased the efficacy of PDT due to the targeted action between HA and cancer cells<sup>66</sup> and the ability of CeNPs to catalyse  $\text{H}_2\text{O}_2$  to produce more  $\text{O}_2$  (ref. 41). In conclusion, various surface modifications based on the CeNPs technology improve adjuvant therapies for PDT and constitute a leap forward to their foreseeable clinical application.

PTT is a highly effective and non-invasive cancer therapy that benefits from the photothermal effects of photothermal transducers (PTA) to collect energy from light and convert it into heat. Thereby, the heat generation raises the ambient temperature and triggering cancer cell death.<sup>67</sup> The cardinal problem with PTT lies in the limited depth of light penetration, and recurrent tumours often occur at the edge of the tumour beyond the limit of laser penetration.<sup>68</sup> Other disadvantages include the relatively low efficiency of PTA delivery in tumours, excessive heat leading to unnecessary damage to healthy tissue, and resistance to PTT due to overexpression of heat shock proteins in some cancers. Thus, current strategies have focused on combining PTT with other cancer therapies, such as PDT.<sup>69,70</sup> On the one hand, PTT-induced heating can improve blood flow and  $\text{O}_2$  content, providing more  $\text{O}_2$  for PDT; on the other hand, PDT increases the sensitivity of cancer cells to heat. However, PTT/PDT alone does not kill cancer cells completely because the heat and  $\text{O}_2$  are not evenly distributed within the tumour. Therefore, it is critical to design a nanosystem with an  $\text{O}_2$  supply function *in situ*. Lingwan Zeng *et al.* synthesised a nanosystem named  $\text{Bi}_2\text{S}_3\text{@Ce6-CeO}_2\text{-x}$  for PTT/PDT treatment.<sup>42</sup> CeNPs can react with excessive  $\text{H}_2\text{O}_2$  in the TMEs, producing a large amount of  $\text{O}_2$  to improve the hypoxia condition and thus enhance the efficacy of PTT/PDT. According to experimental results *in vitro* and *in vivo*, PTT/PDT therapy of  $\text{Bi}_2\text{S}_3\text{@Ce6-CeO}_2\text{-x}$  NC has a synergistic therapeutic effect, therefore being better than any single treatment. Another example was reported by Zeng *et al.*, in which recycled  $\text{CeO}_2\text{-x}$  catalase nanozymes and indocyanine green (ICG) were co-loaded into hyaluronic acid nanovesicle to alleviate the hypoxic TMEs and realise the tumour-targeted PTT/PDT.<sup>71</sup> The *in vivo* tests indicated that  $\text{CeO}_2\text{-x}$  could improve the outcomes of PDT by the recycling of cerium valence state, in combination with the PTT effect induced by ICG, providing a desirable therapeutic efficacy in tumour-bearing mice (Fig. 6). Moreover, it is worth noting that PTT, as a non-invasive treatment mode, can also be used cooperatively with chemotherapy to execute a better treatment effect.<sup>72</sup> Studies packed Ru@CeO<sub>2</sub>YSNs with the anticancer ruthenium complex (RBT) and resveratrol (Res) and used REG to construct a double-layered structure to form a dual drug delivery system Ru@CeO<sub>2</sub>-RBT/Res-DPEG.<sup>43</sup> The system can catalyse endogenous  $\text{H}_2\text{O}_2$  to produce oxygen, realizing *in situ* oxygen supply and enhancing chemotherapy and PTT for colorectal cancer. *In vitro* research has found that Ru@CeO<sub>2</sub>-RBT/Res-DPEG has an ideal tissue penetration depth and anticancer effect and inhibits the metastasis and recurrence of colorectal cancer.

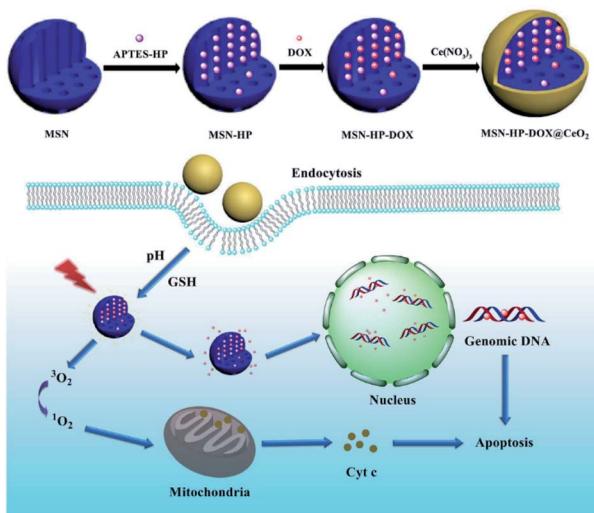


Fig. 5 Schematic demonstration of synthetic and working protocol for triple-stimuli-responsive drug delivery system. DOX was assembled into MSN-HP and then coated with  $\text{CeO}_2$  to form the triple-stimuli-responsive drug delivery system. After endocytosed by cells, the system could respond under the intracellular environment and ultimately, targeted the nucleus and mitochondria to induce apoptosis of cancer cells. Reproduced from ref. 39 with permission from Springer Nature.



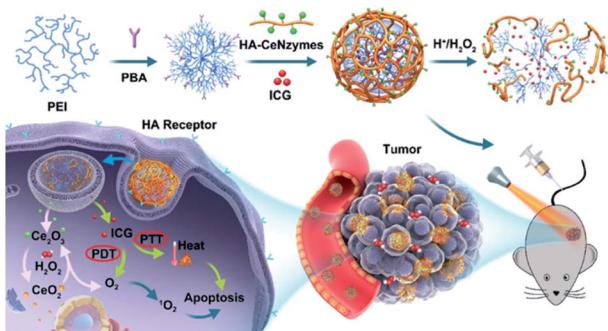


Fig. 6 Schematic illustration of *in vivo* regenerable cerium oxide nanzyme-loaded pH/H<sub>2</sub>O<sub>2</sub>-responsive nanovesicle for tumor-targeted PDT and PTT (PEI, poly(ethylene imine); PBA, 4-carboxyphenylboronic acid pinacol ester; HA, hyaluronate; CeNzymes, CeO<sub>2</sub> nanzyme). PDT and PTT were both marked with red ellipses. This figure was reproduced from ref. 71 with permission from the American Chemical Society.

## Conclusions

In this review, we intensely focus on the application and mechanism of CeNPs in cancer diagnosis and treatment. CeNPs are a great tool as they show excellent potential in biological diagnosis, drug delivery and oncology. The effect of CeNPs depends on the dose, application time, nanometer diameter, cell type and intracellular environment, to cite a few. Furthermore, the toxicity of CeNPs is also dose-dependent and time-dependent in cancer cells, as some studies have shown that high doses of CeNPs may promote the proliferation of hepatocellular carcinoma cells in a dose-dependent manner. Therefore, a compromise is needed to destroy the malignant tissue without affecting the healthy tissue around it. CeNPs face an important issue in conducting clinical trials to explore effectiveness and toxicity, so therefore the selection of CeNPs in cancer treatment should take into account the various circumstances here reviewed. In this regard, extensive research is needed to further investigate the absorption, distribution, metabolism, and related immune responses of nanoparticles. This guide provides advice for the application of biological antioxidant nanomaterials to cancer treatment.

## Author contributions

Na Feng and Ying Liu: literature collection and evaluation, and manuscript preparation; Xianglin Dai and Yingying Wang: figure legend preparation, references insertion, and graphic abstract preparation; Qing Li and Qiong Guo: concept development idea generation, and manuscript editing and revision.

## Conflicts of interest

There are no conflicts to declare.

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